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10/535,267

11/22/2005

Kevin J. Tracey

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EXAMINER

BLANCHARD, DAVID J

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PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No. 10/535,267	Applicant(s) TRACEY, KEVIN J.	
	Examiner David J. Blanchard	Art Unit 1643	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 27 May 2008.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-45 is/are pending in the application.
- 4a) Of the above claim(s) 10-45 is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1-9 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☒ The specification is objected to by the Examiner.
- 10) ☒ The drawing(s) filed on 17 May 2005 is/are: a) ☒ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413) |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | Paper No(s)/Mail Date. _____ |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08) | 5) <input type="checkbox"/> Notice of Informal Patent Application |
| Paper No(s)/Mail Date <u>6/5/06</u> . | 6) <input type="checkbox"/> Other: _____ |

DETAILED ACTION

1. The preliminary amendments filed 17 May 2005 and 28 August 2006 have been entered in full.

Election/Restrictions

2. Applicant's election with traverse of the invention of Group I, claims 1-9 in the reply filed on 27 May 2008 is acknowledged. The traversal is on the grounds that the claims of the present application were searched during the PCT phase and did not receive a unity of invention objection, citing MPEP 1893.03 and 37 CFR 1.475(b) for support. Applicant states that Groups I and III require a polypeptide comprising an HMGB B box or a functional variant thereof and hence a search of Groups I and III has substantial overlap and can be made without a serious burden on the Examiner. This is not found persuasive because 37 CFR 1.499 (MPEP 1893.03(d)) provides that an examiner **may** require the restriction of claims for a national stage application that lacks unity of invention under §1.475. Applicants' MPEP citation merely states that once the national stage has been taken up by the examiner, prosecution proceeds in the same manner as for a domestic application (e.g., US application in this case) with the exception that unity of invention proceeds under 37 CFR 1.475, which states that where a group of inventions is claimed in an application, the requirement of unity of invention shall be fulfilled only when there is a technical relationship among those inventions involving one or more of the same or corresponding special technical features. The expression "special technical features" shall mean those technical features that define a contribution which each of the claimed inventions, considered as a whole, makes over the prior art. In view of the prior art applied in the instant Office Action (see below), Applicants' special technical feature recited in claim 1 (a polypeptide comprising an HMGB B box) does not define a contribution over the prior art and hence is not 'special'. Hence, there is no technical relationship left over the prior art among the claimed inventions involving one or more of the same or corresponding special technical features, leaving two or more dependent claims without a single general inventive

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concept. Applicant is reminded that search burden is not relevant to unity of invention, however, as evident by the prior art applied in the instant Office Action a search and examination of Groups I and III is not coextensive.

The requirement is still deemed proper and is therefore made FINAL.

3. Claims 10-45 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim.

4. Claims 1-9 are under consideration.

Information Disclosure Statement

5. The information disclosure statement (IDS) submitted on 05 June 2006 has been fully considered by the examiner. A signed and initialed copy of the IDS is included with the instant Office Action.

Specification

6. The title of the invention is not descriptive. A new title is required that is clearly indicative of the invention to which the claims are directed. Applicant should restrict the title to "HMGB Polypeptides for Increasing Immune Responses", for example.

Appropriate correction is required.

Claim Rejections - 35 USC § 112

7. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

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8. Claims 1-9 are rejected under 35 U.S.C. 112, first paragraph, while being enabling for a composition comprising a polypeptide comprising an HMGB B box comprising the amino acid sequence of SEQ ID Nos:5, 20 or 45 and does not comprise an HMGB A box, wherein the HMGB B box is mammalian, human or is a HMGB1 B box and further comprising an adjuvant, does not reasonably provide enablement for a pharmaceutical composition comprising a therapeutically effective amount of a polypeptide comprising an HMGB B box or a functional variant thereof and does not comprise an HMGB A box, wherein said polypeptide increases an immune response in an individual administered said pharmaceutical composition and wherein the HMGB B box is mammalian, human or is a HMGB1 B box and the pharmaceutical composition further comprises a vaccine, or an adjuvant selected from one or more immunostimulatory oligonucleotides comprising unmethylated CpG sequences, an imidazoquinoline, monophosphoryl lipid A and detoxified lipopolysaccharide as broadly encompassed by the claims. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make or use the invention commensurate in scope with these claims.

Factors to be considered in determining whether a disclosure meets the enablement requirement of 35 USC 112, first paragraph, have been described by the court in *In re Wands*, 8 USPQ2d 1400 (CAFC 1988).

Wands states on page 1404,

"Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized by the board in *Ex parte Forman*. They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims."

The claims are broadly drawn pharmaceutical composition comprising a therapeutically effective amount of a polypeptide comprising an HMGB B box or a functional variant thereof and does not comprise an HMGB A box, wherein said polypeptide increases an immune response in an individual administered said pharmaceutical composition and wherein the HMGB B box is mammalian, human or is a

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HMGB1 B box and the pharmaceutical composition further comprises a vaccine, or an adjuvant selected from one or more immunostimulatory oligonucleotides comprising unmethylated CpG sequences, an imidazoquinoline, monophosphoryl lipid A and detoxified lipopolysaccharide.

The specification discloses that a HMGB B box comprises a human HMGB1 B box comprising SEQ ID NO:5, 20 or 45 (which are three different lengths of the human HMGB1 B box) (e.g., see pg. 11). The specification discloses that HMGB B box polypeptides of the invention also encompass sequence variants and functional variants, including allelic variants and variants having at least 60% sequence identity to the disclosed HMGB B box (e.g., at least 60% sequence identity to SEQ ID Nos:5, 20 and 45) (e.g., see pp. 12-13). The specification discloses that the HMGB B box polypeptide and pharmaceutical compositions comprising such can be used to increase an immune response in an individual and to treat a number of diseases, including cancer and viral infections (e.g., HIV/AIDS), allergic disease and asthma and can be used as part of a vaccine (e.g., see pp. 2-3 and 14-15). Thus, the claim terminology embraces a large genus of structural and functional variants and the use of HMGB B box polypeptides as part of a pharmaceutical composition and as a vaccine for the treatment and/or prevention of cancer and viral infections.

The specification teaches the cloning of human HMGB1 and truncated forms of HMGB1 containing the B box motif when demonstrate potent induction of TNF production (see examples). The specification does not teach the genus of HMGB B box polypeptides and functional variants thereof that induce an immune response and treat or prevent cancer or a viral infection (e.g., HIV/AIDS). There are no working examples of a HMGB B box polypeptide or functional variant thereof that induces an immune response and treats or prevents cancer or a viral infection. Thus, the scope of the claims is extremely broad compared to the guidance and exemplification provided in the specification. The scope of the claims must bear a reasonable correlation with the scope of enablement. See *In re Fisher*, 166 USPQ 19 24 (CCPA 1970).

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With respect to the genus of polypeptides comprising an HMGB B box or a functional variant thereof, the state of the prior art is such that protein chemistry is probably one of the most unpredictable areas of biotechnology. For example, Skolnick et al (Trends in Biotechnology, 18(1):34-39, 2000) teach that the skilled artisan is well aware that assigning functional activities for any particular protein or protein family based upon sequence. Metzler et al (Nature Structural Biology, 4:527-531, 1997) show that any variety of single amino acid substitutions can alter or abolish the ability of CTLA4 to interact with its ligands CD80 and CD86 (e.g., summarized in Table 2). For example, Mikayama et al. (Proc. Natl. Acad. Sci., USA, 90:10056-10060, 1993) teach that the human glycosylation factor (GIF) protein differs from human macrophage migration inhibitory factor (MIF) by a single amino acid residue (see Figure 1 in particular). Yet, Mikayama et al. further teach that GIF is unable to carry out the function of MIF and MIF does not demonstrate GIF activity (see Abstract in particular). Burgess et al (J Cell Biol. 111:2129-2138, 1990) show that a conservative replacement of a single "lysine" residue at position 118 of acidic fibroblast growth factor by "glutamic acid" led to the substantial loss of heparin binding, receptor binding and biological activity of the protein homology is inaccurate, in part because of the multifunctional nature of proteins (e.g., "Abstract" and "Sequence-based approaches to function prediction", page 34).

With respect to a pharmaceutical composition comprising polypeptides comprising an HMGB B box or functional variants thereof for therapeutic applications, the state of the prior art also recognizes that the administration of an HMGB1 polypeptide triggers an inflammatory cascade, which activates inflammatory responses that can cause tissue damage and even death. See Fig. 4 of Yang et al (Journal of Leukocyte Biology, 78:1-8, July 2005). Yang et al also teach that administration of HMGB1 into mice joints induces arthritis changes and stimulated the synovial macrophages to release proinflammatory cytokines including TNF, IL-1 β and IL-6, indicating that HMGB1 plays a pathogenic role in arthritis (pg. 5). Andersson et al (Journal of Leukocyte Biology, 72:1084-1091, December 2002) teaches that HMGB1 is a mediator of acute inflammatory lung injury and to elucidate the importance of

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extracellularly released HMGB1 in the pathogenesis of human diseases and to plan for future therapeutic intervention, there are a number of basic questions to resolve (see pg. 1089, "Lung Inflammation" and "Future Perspectives"). Andersson et al also poses the question, will HMGB1 be validated as a clinical target, like TNF or IL-1, to modulate acute or chronic inflammation, or will it be too dangerous to interfere with a molecule that is so central for the interplay between necrotic cell death with subsequent inflammation and repair response? (see pg. 1090). With respect to the administration of a pharmaceutical composition comprising an HMGB B box polypeptide further comprising a vaccine and, in turn, preventing cancer in a patient, reasonable guidance with respect to preventing any cancer relies on quantitative analysis from defined populations, which have been successfully pre-screened and are predisposed to particular types of cancer. This type of data might be derived from widespread genetic analysis, cancer clusters, or family histories. The essential element towards the validation of a preventive therapeutic is the ability to test the drug on subjects monitored in advance of clinical cancer and *link* those results with subsequent histological confirmation of the presence or absence of disease. This irrefutable link between antecedent drug and subsequent knowledge of the prevention of the disease is the essence of a valid preventive agent. Further, a preventive administration also must assume that the therapeutic will be safe and tolerable for anyone susceptible to the disease. The goal of tumor vaccination is the induction of tumor immunity to prevent tumor recurrence and to eliminate residual tumorous disease. It is well known in the art that tumor cells in vivo simply do not display their unique antigens in ways that are easily recognized by cytotoxic T lymphocytes (Ezzell; page 48, column 2, paragraph 2; The Journal of NIH research, 7:46-49, January 1995). Forni et al (Cancer Research, 2000, 60; 2571-2575) disclose tumor cells have the ability to escape immune reactions and tumor masses can suppress immune attack (see page 2571, right column). Mouse models show that elicitation of a significant immune response in patients with advanced tumors is exceedingly difficult, and only a minority of tumor-bearing mice are cured. "As a tumor increases in size, it becomes refractory to immunotherapy" (see page 2571, left column). A similar picture is emerging from Phase I immunotherapy trails where only a

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few patients with established tumors display objective and in any event temporary responses (see page 2571, right column). Tumor burden and antigenic drift continue to present serious burdens for successful cancer therapy *in vivo*. Tumors are classified as immunogenic or non-immunogenic, solid or hematological in nature. Effective cancer strategies should be designed to deal effectively with the nature of each of these classifications.

Donnelly J. (Nature Medicine, 11(9): 1354-1356, Nov. 2003) states “treating cancer with something that looks more like a modern-day vaccine, with a defined antigen and an optimized adjuvant and delivery platform, is still in the future” (see page 1354 lines 13-17). Further, DeGruijl T. D. et al (Nature Medicine, 5(10): 1124-1125, Oct. 1999) state that a variety of anti-tumor vaccine trials have been undertaken and in spite of the large number of these trials, and the plethora of distinct approaches investigated, there has been little evidence of clinical efficacy. DeGruijl also states “precise correlates of clinical effects and immunological responses have been lacking” (see page 1124, left column). It is unlikely that a pharmaceutical composition comprising a polypeptide comprising an HMGB B box or functional variant thereof would provide a therapeutic benefit in cancer patients or patients having a viral infection. There is no guidance or direction to assist the skilled artisan in using a pharmaceutical composition comprising just any HMGB B box polypeptide, including HMGB B box polypeptide variants and functional variants, including allelic variants and variants having at least 60% sequence identity to the disclosed HMGB B box (e.g., at least 60% sequence identity to SEQ ID Nos:5, 20 and 45) for the treatment of cancer or a viral infection, nor is there any guidance or direction for the use of said pharmaceutical compositions as a vaccine for the prevention of cancer or a viral infection. Applicants provide little or no guidance beyond the mere presentation of sequence data to enable one of skill in the art to determine, without undue experimentation, the positions in the disclosed HMGB B box polypeptides of SEQ ID Nos:5, 20 and 45 that are tolerant to change and the nature and extent of changes that can be made in these positions. Additionally, the specification does not define or experimentally determine a “therapeutically effective amount” of the claimed pharmaceutical compositions,

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optionally further comprising a vaccine that would provide a therapeutic benefit in cancer or HIV/AIDS patients, which is particularly critical to practicing the claimed pharmaceutical composition in view that HMGB1 triggers an inflammatory cascade, which activates inflammatory responses that can cause tissue damage and even death, HMGB1 plays a pathogenic role in arthritis and is implicated in acute inflammatory lung injury. Further, with respect to HMGB1 as a clinical target, the art (Andersson et al, supra) questions whether it will be too dangerous to interfere with HMGB1, which is so central for the interplay between necrotic cell death with subsequent inflammation and repair response. One of ordinary skill in the art could not predictably extrapolate the teachings, guidance and exemplification in the specification limited to HMGB B box polypeptides comprising a human HMGB1 B box comprising SEQ ID NO:5, 20 or 45 (which are three different lengths of the human HMGB1 B box) and which potentially induce TNF production to the full scope of the claims encompassing pharmaceutical compositions comprising a large genus of HMGB B box polypeptides and functional variants thereof (i.e., at least 60% identity) that induce an immune response and are useful for the treatment and/or prevention of cancer or a viral infection (e.g., HIV/AIDS). One of skill in the art would neither expect nor predict the appropriate functioning of the pharmaceutical compositions as broadly as is claimed.

In view of the lack of the predictability of the art to which the invention pertains as evidenced by Skolnick et al, Metzler et al, Mikayama et al, Burgess et al, Yang et al, Andersson et al, Ezzell et al, Forni et al, Donnelly J. and DeGrujil et al, the lack of guidance and direction provided by applicant, and the absence of working examples, undue experimentation would be required to practice the claimed HMGB B box pharmaceutical compositions and vaccines with a reasonable expectation of success, absent a specific and detailed description in applicant's specification of how to effectively practice the claimed HMGB B box pharmaceutical compositions and vaccines and absent working examples providing evidence which is reasonably predictive that the claimed HMGB B box pharmaceutical compositions and vaccines are therapeutically effective, commensurate in scope with the claimed invention.

Claim Rejections - 35 USC § 102

9. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

(e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

10. Claims 1-2 and 4-5 are rejected under 35 U.S.C. 102(a) as being anticipated by Taudte et al (Protein Engineering, 14(2):1015-1023, December 2001, IDS reference C69 filed 6/5/06).

Then claims are drawn to a pharmaceutical composition comprising a therapeutically effective amount of a polypeptide, wherein said polypeptide comprises or consists of an HMGB B box or a functional variant thereof and does not comprise an HMGB A box and wherein said polypeptide increases an immune response in an individual administered said pharmaceutical composition, wherein the HMGB B box is mammalian. Applicant is reminded that the intended use of a product claim carries no patentable weight. See MPEP 2111.02. Thus, the intended use of the claimed composition as a pharmaceutical composition is given no patentable weight.

Taudte et al teach rat HMG1 B box protein compositions that contain the HMG1 B box and do not comprise the HMG1 A box (e.g., see entire document, particularly pp. 1016-1018, and Figs. 1-2). Applicant is reminded that products of identical chemical composition can not have mutually exclusive properties. A chemical composition and its properties are inseparable. Therefore, if the prior art teaches the identical chemical structure, the properties applicant discloses and/or claims are necessarily present. *In re Spada* 15 USPQ2d 1655, 1658 (Fed. Cir. 1990). See MPEP 2112.01.

Thus, Taudte et al anticipates the claims.

11. Claims 1-2 and 4-5 are rejected under 35 U.S.C. 102(b) as being anticipated by Bianchi et al (The EMBO Journal, 11(3):1058-1063, 1992, IDS reference C11 filed 6/5/06).

Bianchi et al teach rat HMG1 B box protein compositions that contain the HMG1 B box and do not comprise the HMG1 A box (e.g., see entire document, particularly pp. 1058 and Fig. 4). Applicant is reminded that products of identical chemical composition can not have mutually exclusive properties. A chemical composition and its properties are inseparable. Therefore, if the prior art teaches the identical chemical structure, the properties applicant discloses and/or claims are necessarily present. *In re Spada* 15 USPQ2d 1655, 1658 (Fed. Cir. 1990). See MPEP 2112.01.

Thus, Bianchi et al anticipates the claims.

12. Claims 1-5 and 7 are rejected under 35 U.S.C. 102(e) as being anticipated by Tracey et al (Us 2003/0144201 A1, priority to 5/15/2001, IDS reference A6 filed 6/5/06).

The applied reference has a common inventor with the instant application. Based upon the earlier effective U.S. filing date of the reference, it constitutes prior art under 35 U.S.C. 102(e). This rejection under 35 U.S.C. 102(e) might be overcome either by a showing under 37 CFR 1.132 that any invention disclosed but not claimed in the reference was derived from the inventor of this application and is thus not the invention "by another," or by an appropriate showing under 37 CFR 1.131.

Claims 1-2 and 4-5 have been described supra.

Claims 3 and 7 recite wherein the HMGB B box is human and wherein the pharmaceutical composition further comprises an adjuvant.

Tracey et al teach pharmaceutical compositions that contain a human HMGB1 b box polypeptide of SEQ ID NO:5 (e.g., does not comprise an HMGB A box) and wherein the polypeptide induces the release of a pro-inflammatory cytokine from a vertebrate

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cell or increases inflammation and Tracey et al teach the HMGB1 B box fused to keyhole limpet hemocyanin (KLH) for increasing the immunogenicity of the B box for the production of anti-B box antibodies and hence, KLH is reasonably interpreted to be an adjuvant (see entire document, particularly par. 0017, 0099 and pp. 11-13).

Thus, Tracey et al anticipate the claims.

13. No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to David J. Blanchard whose telephone number is (571) 272-0827. The examiner can normally be reached at Monday through Friday from 8:00 AM to 6:00 PM, with alternate Fridays off. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry Helms, can be reached at (571) 272-0832.

The official fax number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/David J. Blanchard/
Primary Examiner, A.U. 1643